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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,984	01/04/2002	Yin-Xiong Li	275.0003 0102	9705
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/038,984	LI ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 19 July 2010.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 75,76,78,79,82,83 and 85-121 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 75,76,78,79,82,83 and 85-121 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4 documents</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 19, 2010 has been entered.

Claim Rejections - 35 USC § 112

Claims 75, 76, 78, 79, 82, 83, 85-98 and 121 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of double stranded RNAs of a length greater than 141 base pairs to inhibit GFP, Zf-T, Pax 6.1 and NKx 2-7 in zebrafish embryos, use of double stranded RNAs of a length greater than 201 base pairs to inhibit HirA in chick neural crest explants and use of double stranded RNAs of a length greater than 187 base pairs to inhibit GFP in NIH3T3 cells, does not reasonably provide enablement for use of double stranded RNAs targeted to any other foreign, endogenous or pathogen genes in all types of vertebrate cells. The specification further does not reasonably provide enablement for an *ex vivo* method that includes treatment of an explanted cell with dsRNA followed by implantation into an

organism and does not reasonably provide enablement for using this *ex vivo* method to treat a disease or pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The nature of the invention and the breadth of the claims

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA, and implanting the cell into a vertebrate organism. In the embodiments of claims 96-98, the target gene is associated with a disease or pathogen. In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromosomal; the function of the target gene may be unknown. The claims are further directed to a method that identifies a phenotypic change in the treated cell.

The amount of direction provided by the inventor and the existence of working examples

The specification teaches at page 2 that the present invention allows for attenuation of gene expression in a cell and teaches that inhibition of gene function is evidenced by a reduction or elimination of the activity associated with the protein encoded by the target gene. The specification further teaches at page 2 that the attenuation of gene expression is specific for the targeted gene. The specification contemplates a method of treating or preventing disease or infection in a mammal and teaches at page 4 that the methods of the invention can be used to target an endogenous gene or a pathogen gene for medical applications. The specification also states that the method could be used to treat disease or infection, providing general guidance at pages 15-16 of how the RNA would be delivered to the cell and that endogenous or pathogen genes can be targeted, but provides no specific guidance how to overcome the art recognized problems associated with use of transplanted cells.

The working examples of the specification describe the use of dsRNA to inhibit expression of several well-characterized genes, including two reporter genes (GFP and Zf-T) in zebrafish embryos. Each of these examples uses long double stranded RNAs: GFP is targeted with dsRNA of 187 base pairs, Zf-T is targeted with dsRNA of 321 base pairs, Pax 6.1 is targeted with dsRNA of 298 base pairs and Nkx 2-7 is targeted with dsRNA of 141 base pairs. Further working examples describe the use of dsRNA of 201 base pairs targeted to HirA in explanted chick neural crest tissue and the use of dsRNA of 187 base pairs targeted to the reporter gene GFP in NIH3T3 cells. None of the working examples describe *ex vivo* treatment of a cell followed by implantation into any organism for any purpose.

The specification teaches that the instant invention provides a method of attenuating gene expression and states that this attenuation is specific for the targeted gene; however, those in the art were aware that administration of dsRNA to vertebrate cells results in a non-specific response that leads to general suppression of protein synthesis and cell apoptosis. The working examples of the specification use long dsRNA that would be expected to produce this response. There is no disclosure in the specification regarding how to overcome the non-specific effects reported in the prior art when double stranded RNAs are added to vertebrate cells.

The state of the prior art, the level of ordinary skill in the art and the level of predictability in the art

The level of ordinary skill in the art is high, however there are several aspects of the invention that are unpredictable in view of the disclosure of the instant specification and the knowledge found in the prior art. These aspects include the limited applicability of the results observed in the specification's working examples to the broad scope of the claims, the unpredictability of RNA interference in vertebrate cells and the unpredictability of using transplanted cells comprising dsRNA for the purpose of treating disease.

Most organisms exhibit an immune response (termed the PKR response) that results in non-specific translation arrest and is triggered by even small amounts of double stranded RNA. This response has precluded the use of dsRNA *in vivo* to specifically attenuate gene expression and the unpredictability of specifically attenuating expression of a target gene in vertebrate cells by RNA interference (RNAi) is evident in

both pre-filing and post-filing art, particularly with regard to avoidance of this response. This unpredictability extended for at least a year after the filing date.

The specification describes working examples wherein RNA interference is performed in zebrafish embryos, explanted chick neural crest tissue and cultured rodent cells. These experiments use dsRNAs ranging in size from 141-298 base pairs to target both reporter genes and endogenous genes and describe that the targeted gene is attenuated specifically.

However, these results are directly contradictory to what the skilled artisan would expect. For example, Oates et al. (Developmental Biology 2000, of record) teaches that dsRNA injected into early zebrafish embryos produced a nonspecific depletion of several endogenous mRNAs and concluded that "RNAi appears unsuited to application in the zebrafish embryo" (page 21, left-hand column).

Zhao et al. (Developmental Biology 2001, of record) also report that injection of dsRNA results in degradation of endogenous mRNA and has a nonspecific effect at the posttranscriptional level.

Caplen et al. (Gene 2000, of record) teach that despite the existence of evidence of co-suppression (another term for RNAi), transfection of dsRNA into mouse NIH 3T3 cells transduced with a retrovirus expressing β gal induced no detectable decrease in gene expression (see pages 102-103). Caplen et al. further teach it is possible that gene, cell-type, or developmentally specific effects influence the balance between specific and non-specific responses to dsRNA. Caplen et al. note that these possibilities would need to be taken into account when considering RNAi in mammalian cell systems.

The use of suitable models is critical in order to predictably extrapolate experimental results to other cell types, but the results observed in the examples are not broadly applicable to all vertebrate cells. While RNAi has been observed in other vertebrate embryo systems, those in the art question the general applicability of these results. Wianny et al. (Nature Cell Biology 2000, of record) reported that dsRNA can be used as a specific inhibitor of gene activity in the mouse oocyte (targeting c-mos) and preimplantation embryo (targeting E-cadherin or a GFP transgene) without causing a general translation arrest. However, the authors indicate (see page 73, under Discussion) that it is possible the early mouse embryo is incapable of the interferon response that would result in general translation arrest and that there may still be difficulties in using RNAi at later stages.

More than a year after the filing date of this application, the field of RNA interference determined that shorter dsRNA molecules of 21-23 nucleotides could avoid the PKR response in vertebrate cells and provide a more predictable inhibitory response. Elbashir et al. (Nature 2001, of record) recognized the importance of avoiding the PKR response, stating at page 494,

“...it is known that dsRNA in the cytoplasm of mammalian cells can trigger profound physiological reactions that lead to the induction of interferon synthesis. In the interferon response, dsRNA> 30 bp binds and activates the protein kinase PKR and 2', 5'- oligoadenylylate synthetase (2', 5' -AS).”

Elbashir et al. confirmed this by demonstrating that introduction of long dsRNAs into NIH3T3 cells non-specifically reduced reporter-gene expression (see page 496, first column). In further experiments Elbashir et al. were able to show for the first time that shorter dsRNAs avoided this non-specific response and effectively inhibited gene expression in a manner specific to the target gene.

Although it was well known in the art that RNA of greater than 30 base pairs induces the PKR response the working examples describe experiments using RNAs that are much longer; having a length of at least 141 base pairs. The specification briefly contemplates at page 12 that the RNA used in the method can be as short as 25 base pairs but aside from the discussion at page 34 the specification provides no discussion of the PKR response, provides no discussion of how to avoid this response and provides no specific guidance regarding length of the RNA that would direct the skilled artisan to the use of shorter dsRNAs as a way to overcome the PKR response.

The examples provided in the specification are not commensurate with the claims, which are directed to RNA interference performed in any vertebrate cells. The examples use long dsRNA, known to those in the art to induce the PKR response. While the working examples appear to avoid this response the art clearly suggests that administering dsRNA to vertebrate systems, either *in vitro* or *in vivo*, to attenuate target genes is not a reproducible or predictable art because one would expect long dsRNAs to non-specifically inhibit gene expression.

Claims 96-98 are additionally directed to treatment of disease by transplanting cells wherein the targeted gene is associated with a disease or with a pathogen such as a virus or bacterium. While the specification contemplates at pages 15-16 that the disclosed methods can be performed *ex vivo* and can be used to treat disease, there is no specific guidance regarding how treatment is to be performed. The specification provides no working examples describing targeting of any disease or pathogen gene and provides no examples wherein a cell treated *ex vivo* is implanted into an organism for the purpose of treating any disease.

Coburn et al. (Journal of Antimicrobial Chemotherapy 2003, of record) point out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example page 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes several years after the time of invention that therapeutic methods are not yet effective.

The quantity of experimentation needed to make the invention based on the content of the disclosure

At the time of filing, those of skill in the art were well aware of the non-specific PKR response induced by administration of dsRNA to vertebrate cells which leads to a general suppression of protein synthesis and cell apoptosis. Because the results of the experiments described in the working examples are not generally applicable to all vertebrate cells, one of ordinary skill in the art would not have believed the methods disclosed in the instant specification would produce sequence-specific inhibition of gene expression in vertebrate cells because the administered dsRNA would be expected to activate mechanisms including the PKR kinase and inhibit all gene expression. While those in the art have subsequently determined that dsRNAs of shorter length will provide specific inhibition of expression, the specification provides no specific guidance regarding the length or RNA to be used; merely contemplating that RNAs of 25-400 bases are useful. Therefore in order to perform the claimed invention throughout its full

scope at the time of filing the skilled artisan would have had to perform trial and error experimentation to discover the length of RNAs that will provide specific attenuation of expression in all vertebrate cells.

Despite the general knowledge of the PKR response, the instant specification provides no specific guidance of how this response is to be overcome. Because the prior art teaches that administration of dsRNA to vertebrate systems is not a reproducible or predictable art in order to practice the instantly claimed invention throughout its entire scope the skilled artisan would have to engage in undue, trial and error experimentation to determine which genes can be attenuated in the exemplified cells and this experimentation would have to be repeated for each type of cell in which the claimed method is to be performed in order to determine which genes can be attenuated using dsRNA without inducing the interferon response.

For targeting of disease or pathogen genes, one of skill in the art would have to further experiment to determine what disease genes can be inhibited by transplanted cells in order to provide a therapeutic effect.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of introducing any dsRNA for any target gene in any vertebrate cell followed by transplantation into an organism because the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Because one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation the claims are not enabled.

Response to Arguments

Applicants state they believe the examples present evidence of the claimed invention using a sufficient number of genes and species of vertebrate cells in order to support the claimed genus. Applicants note they have shown successful gene silencing using dsRNA in a wide range of systems targeting a wide range of genes, and have provided numerous working examples.

This argument is not persuasive because as noted in the rejection these examples are not sufficient to overcome the lack of guidance regarding predictability of RNA interference in the species tested, the lack of guidance for overcoming the PKR response and how to use the claimed methods to treat disease.

Applicants have also submitted a declaration by inventor Li. Dr. Li expresses the opinion that the results reported in the Oates and Zhao references do not support the conclusion that injection of dsRNA into zebrafish embryos causes non-specific effects. Dr. Li submits that the results can be explained by physical damage to the embryos although the declaration also characterizes injection of zebrafish embryos as routine. Dr. Li further states the results can also be explained by use of organic solvents and high levels of sodium.

While the examiner recognizes Dr. Li is knowledgeable in the field of zebrafish embryos and has an alternative explanation for the results described in the Oates and Zhao references, the examiner notes these references appear in peer-reviewed journals and the Office has no way of determining if these alternatives explanations were examined during the review process. The description of possible problems set out in the declaration with regard to experiments in zebrafish embryos also supports the conclusion that the level of enablement of the instant claims is low considering the

myriad technical difficulties that can arise when performing experiments in these embryos.

However, even if there is an alternative explanation for the results reported in the Oates and Zhao references, the examiner further notes that the alternative explanation does not overcome the rejection because it does nothing to address the full scope of the claims at issue, which are not limited to zebrafish embryos, or the other issues raised in the rejection.

Applicants argue the zebrafish is designed to be representative of the claimed genus of vertebrate organisms, noting that many experts use it as a model organism. While zebrafish may be a model organism for studies of vertebrate development, this fact does not by itself mean it is representative of all vertebrates for RNA interference.

Applicants argue that despite the contradictory results in Wianny, the skilled artisan could apply the results reported in the specification to other cell types of other vertebrate species without undue experimentation.

This is not persuasive because applicants' data does not show that RNA interference is predictable in the organisms they studied, much less in other species. Wianny's statement reflects the prevailing view at the time, that use of dsRNA in vertebrates to provide specific attenuation of expression is not predictable.

Applicants assert there are large quantities of post-filing art that support predictability.

This argument is not persuasive because this art is based on essential discoveries made after the time of filing of the instant application, specifically the seminal discovery by Elbashir noted in the rejection that predictable use of dsRNA in

vertebrate cells requires RNA of much shorter lengths than the 140+ basepairs used in the working examples.

Applicants assert that the '635 provisional application exemplifies *ex vivo* treatment and that based on this undue experimentation is not required to practice an *ex vivo* method to treat a disease or pathogen.

This is not persuasive because this example was for the study of development, not for treatment of disease. While the examiner recognizes that one could remove a cell, treat it with dsRNA and implant the treated cell back into an organism, this does not demonstrate treatment of a disease. While the treated cell(s) may have reduced expression, the specification provides no guidance how this affects the untreated cells, therefore this example does not provide enablement for treatment of a disease or pathogen.

Applicants state they do not believe undue experimentation would be necessary to practice the invention as claimed, noting that methods for explanting a cell from a vertebrate organism are known to those skilled in the art; that in order to attenuate expression the nucleotide sequence of the gene can be obtained from a database and that both this sequence and a complementary sequence can be synthesized by routine methods and supplied to the cell with routine methods; and that implantation into a vertebrate organism is also routine. Based on these steps applicants conclude the instant claims are fully enabled.

These arguments are not persuasive because they ignore the required outcome of the claimed method. While it is correct that removal of cells, synthesis of RNA and implantation of cells are all routine, obtaining the required outcome, specific attenuation

of the target gene, is not routine for the reasons outlined in the rejection: specifically that the results observed in the specification are not commensurate with the broad scope of the claims, the unpredictability of RNA interference in vertebrate cells due to the presence of the PKR response and the unpredictability of using transplanted cells comprising dsRNA for the purpose of treating disease.

Claim Rejections - 35 USC § 103

Claims 75, 76, 78, 79, 82, 83 and 85-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (of record) in view of Ekenberg et al. (of record).

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA and implanting the cell into a vertebrate organism. Specific embodiments recite that the cell is implanted in the same organism, the RNA is less than 200 bases, the RNA comprises at least 25 nucleotides complementary to the target and the RNA is supplied by expression from a DNA sequence or direct delivery. In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromosomal; the function of the target gene may be unknown or it may be associated with a disease or a pathogen such as a virus, bacterium, fungus or protozoan. In other embodiments the method is performed *in vitro*. The RNA may be comprised of a single, self-complementary strand or two strands that may be annealed in the presence of potassium chloride and may be treated with RNase prior to delivery. The claims are also directed to a method that further comprises identifying a phenotypic change in the treated cell.

Fire et al. teach a method of inhibiting gene expression using a double stranded RNA. At column 10, lines 12-14 the invention is taught as including methods performed in cells *ex vivo* (explanted cells) and subsequently implanted into an organism. At column 8 the method is taught as being performed in vertebrates. The genes targeted can be an endogenous gene or a transgene, which is a foreign gene, or can be from a pathogen (see column 6, lines 45-49). At column 7, lines 42-51 Fire et al. teach that the amount of RNA delivered to a cell can be varied and that both high and low doses may be desirable for particular applications. Fire et al. teach at column 7, line 67-column 8 line 6 the limitations on hybridization conditions and length recited in the claims; the dsRNAs used in the disclosed examples were purified without phenol and chloroform. The dsRNA can be formed from 1 or 2 strands (see column 4, lines 41-46). The method of Fire et al. can be used to treat disease and the dsRNAs can be delivered via several different means (see column 9, lines 48-64). At column 9 Fire et al. teach that the RNA can be purified before administration to a cell. Fire et al. do not teach the use of RNase to purify the double stranded RNA prior to administration.

It was well known in the art at the time of invention that RNases such as RNase A and RNase T specifically degrade single stranded RNA in the presence of double stranded RNA. See, for example, Ekenberg et al., who describe a protocol for RNase protection assays. This assay involves hybridization of an RNA probe and target, followed by removal of remaining single stranded RNA with an RNase specific for single stranded RNA in order to leave only RNA that is part of a double stranded structure.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use RNA purified by treatment with RNase in the method of

inhibiting gene expression with double stranded RNAs taught by Fire et al. Fire et al. explicitly teach that the amount of RNA delivered to a cell can be varied and those of ordinary skill in the art were well aware of the existence of the interferon response, therefore one of ordinary skill would be motivated to optimize the conditions of reaction (such as RNA amount, length and/or modification) in such a way as to avoid this response. Such optimization would be expected to include the use of an amount that would provide the function of not inducing interferon, particularly in view of applicants' contention that the induction of interferon is dependent on the amount of RNA added. One of ordinary skill in the art would be motivated to purify the RNA used for inhibition of gene expression because Fire et al. specifically suggest use of purified RNA. One of ordinary skill would have been motivated to use an RNase specific for single stranded RNA for purification and would have had a reasonable expectation of success in doing so because the use of single-strand specific RNases in order to distinguish between single and double stranded RNA in RNase protection assays was well known.

Thus, the invention of claims 75, 76, 78, 79 and 82-98 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants argue Fire does not provide an enabling disclosure, asserting that mere passing reference to embryonic stem cells, zebrafish and vertebrates does not enable the attenuation of gene expression in embryonic zebrafish cells or vertebrate cells. Applicants state that *C. elegans* (the species used in Fire's working examples) is a primitive and simple invertebrate that contains only 959 somatic cells, and is usually

grown on petri plates seeded with bacteria. Applicants assert the description of dsRNA administration to this single, simple, invertebrate organism does not provide an enabling disclosure for the claimed methods in embryonic zebrafish cells or vertebrate cells.

These arguments are not persuasive because it appears applicants' arguments that Fire does not have an enabling disclosure are based on the fact that Fire does not provide working examples in the claimed cell type. The examiner notes that enablement does not rest alone on the existence of a working example. Further, Fire provides working examples of administration of dsRNA to an organism with hundreds of cells that is more complex than the exemplified zebrafish embryos, which have far fewer than the 959 cells of *C. elegans*. Fire discloses how RNAs can be supplied to cells; applicant has provided no specific evidence that the methods contemplated in the Fire disclosure could not have been successfully used at the time of filing of the instant specification. In fact, the working examples of the instant specification use methods (injection, soaking of cells with a transfection medium) contemplated by Fire as suitable for introducing dsRNA (see Fire, column 9, lines 49-65).

Applicants further argue that Fire himself expressed doubts about the applicability of this technology to vertebrates in a review published subsequent to the earliest priority date of the present application. These remarks are noted, however as stated in the final rejection mailed December 22, 2006, a prior art reference is presumed to be operable in the absence of factual evidence to the contrary, which as described above has not been provided. Any opinions that might have been expressed by Fire either in this review or in any subsequent speech do not change the contents of the '559 patent disclosure.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita, can be reached on 571-272-2876. The central FAX Number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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